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Editorial Comments

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Endothelin receptor antagonists: a place in the management of essential hypertension?

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Introduction

The endothelin system is a potent endothelial system that controls vascular tone and regulates regional blood flow [1]. Today, three isoforms of the endothelin peptide have been described (endothelin-1, -2 and -3) but most biological effects of endothelin are mediated by the 21 amino acid endothelin-1. In addition to its vascular properties, endothelin influences cell proliferation and extracellular matrix synthesis and contributes to the homeostasis of water and electrolytes by direct effects on the kidney [1]. Endothelin acts through the activation of two specific G-protein-coupled receptors, i.e. endothelin Type A (ETA) and endothelin Type B (ETB) receptors. Stimulation of vascular ETA receptors induces vasoconstriction, whereas activation of vascular ETB receptors promotes vasodilatation. Therefore, the impact of endothelin on vascular tone will depend on the balance between the ETA and ETB receptor activation. Since its discovery, the endothelin system has been implicated in the pathophysiology of several diseases including essential arterial hypertension, pulmonary hypertension, congestive heart failure, acute kidney injury and more recently the progression of chronic kidney diseases (CKDs) [2–5].

Since 1992, several peptidic and non-peptidic endothelin receptor antagonists have been synthesized (Table 1) [6]. Animal studies using these antagonists have provided promising results in different indications but today, except for the management of pulmonary hypertension, the clinical development of endothelin receptor antagonists has been relatively slow and their use for the management of essential arterial hypertension is still under investigation. The purpose of this review is to discuss the potential role of endothelin receptor antagonists in the management of arterial essential hypertension and perhaps in the prevention of the progression of CKDs.

Endothelin receptor blockade in hypertension

Because of its important vascular properties, the endothelin system has naturally been considered as a potential mechanism in the development and maintenance of arterial hypertension. The infusion of exogenous endothelin has indeed been shown to raise blood pressure significantly in animals as well as in humans [7]. The possibility that endothelin generates arterial hypertension was further considered with the observation that two patients suffering from a malignant form of hemangioendothelioma, a vascular tumour-secreting endothelin, presented with marked hypertension [8]. High plasma endothelin concentrations have been measured in malignant hypertension and pregnancy-induced hypertension and also in Afro-Americans [7–10]. At last, a greater vasoconstrictor effect of exogenous endothelin has been found in hypertensive patients when compared to healthy subjects [9].

In animal models, endothelin receptor antagonists are effective in lowering blood pressure in salt-sensitive hypertensive models and in stroke prone and malignant hypertension models [11]. In contrast, endothelin receptor blockade appears to be ineffective in renin-dependent models of hypertension. In addition to lowering blood pressure, endothelin antagonists have been shown to have favourable effects on cardiovascular remodelling, on the incidence of stroke and on the progression of renal lesions in animals [11, 12].

In healthy normotensive subjects, the administration of a non-selective endothelin antagonist decreases peripheral arterial resistances leading to a decrease in blood pressure [13]. However, the infusion of a selective ETB antagonist increases vascular resistances suggesting that the hypotensive effect of non-selective antagonists is due essentially to the blockade of ETA receptors [14].

The first large study in essential arterial hypertension compared the anti-hypertensive efficacy of increasing doses of the non-selective endothelin antagonist bosentan with that of enalapril 20 mg and a placebo [15]. The study was conducted in patients with Stage 1–2 hypertension. In this study, bosentan effectively lowered blood pressure and endothelin receptor blockade was significantly superior to placebo but comparable to enalapril. Interestingly, there was no clear dose–response for the anti-hypertensive effect of bosentan between 500 and 2000 mg. The incidence of side effects essentially headaches, flushes and leg oedema

Table 1. Non-peptide endothelin receptor antagonists and their relative selectivity for endothelin receptors[a]

Drug name	Chemical class	Relative selectivity ETA/ETB
Bosentan	Pyrimidine sulfonamide	20
Tezosentan	Pyrimidine sulfonamide	30
Avosentan	Pyrimidine sulfonamide	50–600
Enrasentan	Carboxylic acid	110
Darusentan	Propanoic acid	130–170
Ambrisentan	Propanoic acid	200
Clazosentan	Pyrimidine sulfonamide	1000–3200
Atrasentan	Carboxylic acid	1860
Sitaxsentan	Heteroarylsufonamide	7000
Edonentan	Biphenylsulfonamide	80 000

[a]Adapted from reference [6].

was significantly higher in the bosentan than in the placebo group. For these reasons, the concept of endothelin receptor blockade in essential hypertension was put aside for a while. Additional studies in essential hypertension have been conducted using darusentan and atrasentan, two ETA selective antagonists. Both ETA receptor antagonists were superior to placebo but these agents were not compared to any recognized anti-hypertensive therapy [16, 17] (Table 2).

More recently, new studies have been conducted in patients with resistant hypertension, i.e. patients with uncontrolled blood pressure despite a triple therapy including a diuretic [18–20]. As there is an important medical need for these high cardiovascular risk patients, endothelin antagonists have been considered an interesting new therapeutic approach in this indication. Indeed, because these patients have a high incidence of cardiovascular complications, the tolerability profile of endothelin antagonists remains favourable when compared with the global risk of target organ damages.

In the DORADO program, the first study demonstrated that the addition of darusentan to a triple therapy was superior to the addition of a placebo [19]. This study included patients with an impaired renal function and proteinuria and the addition of darusentan was also associated with a reduction in urinary protein excretion. Unfortunately, the early favourable results of darusentan in resistant hypertension were not confirmed in the latest study [20]. In this randomized controlled trial, a major placebo effect was observed at Week 14, whereas at Week 8, there was a significant difference between the blood pressure lowering effect of darusentan versus placebo or the alpha blocker, guanfacine. These disturbing results were probably due to technical problems linked to the measurement of office blood pressure. Indeed, when blood pressure was assessed using ambulatory monitoring, which avoids the placebo effect, a marked and significant effect of darusentan was observed [20]. Thus, it seems that ETA receptor blockade can provide clinical benefits in patients with resistant hypertension but these data should be confirmed with additional well-conducted randomized trials. In terms of tolerability profile, the major side effect of darusentan was again fluid retention with a decrease in haematocrit due to haemodilution [18–20].

Endothelin receptor antagonists: a potential role in renal protection?

Endothelin-1 also exerts opposing effects on the kidney associated with the activation of vascular and tubular endothelin receptors [21, 22]. Through renal vascular ETA receptors, endothelin-1 induces a vasoconstriction of renal afferent and efferent arterioles. Thus, infusion of endothelin-1 decreases renal blood flow and glomerular filtration rate and eventually reduces urine flow rate and urinary sodium excretion. A contrario activation of tubular ETB receptors increases urine output and sodium excretion. Thus, blockade of ETA, in contrast to ETB receptor blockade, has been recognized as a potential mean to lower filtration fraction and hence proteinuria. This property of selective ETA receptor blockers was nicely demonstrated in animals and in a small set of patients with CKDs [12, 23–25]. Interestingly, the impact of ETA receptor blockade was more prominent in CKD patients than in healthy subjects suggesting that the contribution of the endothelin system to the regulation of renal haemodynamics is important mainly in patients with renal diseases [22].

In CKD patients, several small studies using different agents have demonstrated that endothelin receptor blockers, essentially ETA receptor blockers, lower blood pressure and/or proteinuria [23, 24, 26–29]. Of note, the anti-proteinuric effect of ETA blockade was observed even in patients already treated with a blocker of the renin–angiotensin system, suggesting an additive effect [30, 31]. In one study, the effect of the endothelin antagonist sitaxsentan on proteinuria was superior to that of a placebo or nidefipine, despite comparable decreases in blood pressure when compared with nifedipine 10 mg [32].

The ability of ETA receptor blockade to lower proteinuria urged investigators to perform a large Phase III study in patients with diabetic nephropathy and proteinuria already on a blocker of the renin–angiotensin system [33]. In this randomized controlled trial, two doses of avosentan (25 and 50 mg) were compared to placebo and the main objectives of the study were the changes in proteinuria and the progression of the diabetic nephropathy. At 6 months, a significant decrease in albumin/creatinine ratio was obtained with both doses of avosentan but not with the placebo. Unfortunately, the impact on the progression of diabetic nephropathy could not be investigated because the study was interrupted prematurely. Indeed, the safety committee reported an increased incidence of fluid overload leading to heart failure in patients receiving the two doses of avosentan [33]. This finding therefore corroborated the observations made previously with other endothelin antagonists as discussed above.

In order to clarify the mechanisms leading to the development of fluid overload with endothelin receptor antagonist, a mechanistic study was designed to investigate the dose-dependent renal effects of avosentan in healthy subjects [34]. The results of this placebo-controlled study demonstrated that avosentan indeed induces fluid and sodium retention at high doses (>10 mg/day) in healthy subjects. The fluid retention leads to a significant weight gain and decrease in haematocrit after 1 week of administration. At lower doses

Table 2. Randomized controlled trials assessing the anti-hypertensive efficacy of endothelin receptor antagonists in essential hypertension[a]

Publication	Population	Length (months)	Antagonist	Drug and dose	ΔBP (mmHg) SBP/DBP	P-value
Krum *et al.* [15]	Stage I–II hypertension ($n = 267$)	1	ETA–ETB	Bosentan 2000	−10.3/−5.7	<0.05
				Enalapril 20	−9.0/−5.8	<0.05
				Placebo	−0.9/−1.8	
Nakow [16]	Stage II hypertension ($n = 387$)	1½	Selective ETA	Darusentan 100	−11.3/−8.3[b]	0.0001
				Placebo	n.a.	
Raichlin [17]	Hypertension and high CV risk ($n = 72$)	6	Selective ETA	Atrasentan 10	−14/7	<0.001
				Placebo	−4/−1	
Black *et al.* [18]	Resistant hypertension ($n = 115$)	2½	Selective ETA	Darusentan 300	−11.5/−6.3[b]	0.015/0.002
				Placebo	n.a.	
Weber *et al.* [19]; DORADO	Resistant hypertension and high CV risk ($n = 379$)	2	Selective ETA	Darusentan 300	−18/−11	<0.0001
				Placebo	−9/−5	
Bakris *et al.* [20]; DORADO-AC	Resistant hypertension ($n = 849$)	2½	Selective ETA	Darusentan	−15/−10	n.s.
				Guanfacine	−12/−6	
				Placebo	−14/−8	

[a]ETA, A receptor of endothelin; ETB, B receptor of endothelin; BP, blood pressure; SBP, systolic blood pressure; DBP, diastolic blood pressure; n.a., not applicable; n.s., not significant.
[b]Placebo subtracted.

(1.5 and 5 mg), this effect was not observed suggesting that it might be linked to the loss of receptor selectivity when high doses of the ETA antagonist are administered. Of note, a decrease in haematocrit upon administration of high doses of avosentan has also been found in anephric rats indicating that other mechanisms than sodium and water retention by the kidney may play a role [35]. We have hypothesized that a drug-induced extravasation of fluid as observed with potent peripheral vasodilators may also contribute to the development of oedema in subjects receiving endothelin antagonists.

Taken together, these data confirm that endothelin receptor blockade can lower proteinuria but the benefits of these drugs may be limited by their tolerability profile. Thus, additional studies with well dosed and highly selective ETA antagonists should be conducted in the future to investigate the real potential of this therapeutic approach for renal protection.

Conclusions

There is increasing evidence that endothelin receptor antagonists have some clinical potential in the management of essential hypertension and probably also to retard the progression of renal diseases. However, at this stage, several issues need to be resolved before this approach can be considered for our patients. Firstly, it is obvious that highly selective ETA receptor antagonists should be developed rather than poorly selective blockers. Indeed, the impact on blood pressure and proteinuria appears to be mediated essentially by ETA receptor blockade. In this respect, it is of major importance to define as precisely as possible the dose–response curve of any new agent in order to avoid a lack of selectivity and thereby increase the side effect profile. Secondly, the development of endothelin receptor antagonists further emphasizes the importance of understanding the mechanisms of the major side effects. Thus, the exact role of ETB receptors in the occurrence of fluid overload needs to be clarified and the precise mechanisms of fluid retention should be investigated further in susceptible patients. Indeed, in the ASCEND trial, it appears that fluid retention was very sensitive to loop diuretics and rapidly reversible. Combining an endothelin antagonist with a diuretic might perhaps be one way to limit the incidence of fluid overload if renal mechanisms are predominant. In any case, it seems too early to abandon the development of endothelin receptor antagonists for the management of cardiovascular and renal diseases as we may miss therapeutic opportunities.

Conflict of interest statement. None declared.

References

1. Rubanyi GM, Polokoff MA. Endothelins: molecular biology, biochemistry, pharmacology, physiology, and pathophysiology. *Pharmacol Rev* 1994; 46: 325–415
2. Barton M, Yanagisawa M. Endothelin: 20 years from discovery to therapy. *Can J Physiol Pharmacol* 2008; 86: 485–498
3. Abraham D, Dashwood M. Endothelin—role in vascular disease. *Rheumatology* 2008; 47 (Suppl 5): v23–v24
4. Kalra PR, Moon JC, Coats AJ. Do results of the ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure) study spell the end for non-selective endothelin antagonism in heart failure? *Int J Cardiol* 2002; 85: 195–197
5. Dhaun N, Goddard J, Webb DJ. The endothelin system and its antagonism in chronic kidney disease. *J Am Soc Nephrol* 2006; 17: 943–955
6. Battistini B, Berthiaume N, Kelland NF *et al.* Profile of past and current clinical trials involving endothelin receptor antagonists: the novel "-sentan" class of drug. *Exp Biol Med (Maywood)* 2006; 231: 653–695
7. Hocher B, Thone-Reineke C, Bauer C *et al.* The paracrine endothelin system: pathophysiology and implications in clinical medicine. *Eur J Clin Chem Clin Biochem* 1997; 35: 175–189
8. Yokokawa K, Tahara H, Kohno M *et al.* Hypertension associated with endothelin-secreting malignant hemangio-endothelioma. *Ann Intern Med* 1991; 114: 213–215

9. Cardillo C, Kilcoyne CM, Waclawiw M *et al.* Role of endothelin in the increased vascular tone of patients with essential hypertension. *Hypertension* 1999; 33: 753–758
10. Ergul A. Hypertension in black patients: an emerging role of the endothelin system in salt-sensitive hypertension. *Hypertension* 2000; 36: 62–67
11. Dussaule JC, Boffa JJ, Tharaux PL *et al.* Endothelin, renal diseases, and hypertension. *Adv Nephrol Necker Hosp* 2000; 30: 281–303
12. Nakamura T, Ebihara I, Fukui M *et al.* Effect of a specific endothelin receptor A antagonist on mRNA levels for extracellular matrix components and growth factors in diabetic glomeruli. *Diabetes* 1995; 44: 895–899
13. Haynes WG, Ferro CJ, O'Kane KP *et al.* Systemic endothelin receptor blockade decreases peripheral vascular resistance and blood pressure in humans. *Circulation* 1996; 93: 1860–1870
14. Strachan FE, Spratt JC, Wilkinson IB *et al.* Systemic blockade of the endothelin-B receptor increases peripheral vascular resistance in healthy men. *Hypertension* 1999; 33: 581–585
15. Krum H, Viskoper RJ, Lacourciere Y *et al.* The effect of an endothelin-receptor antagonist, bosentan, on blood pressure in patients with essential hypertension. Bosentan Hypertension Investigators. *N Engl J Med* 1998; 338: 784–790
16. Nakov R, Pfarr E, Eberle S. Darusentan: an effective endothelin A receptor antagonist for treatment of hypertension. *Am J Hypertens* 2002; 15: 583–589
17. Raichlin E, Prasad A, Mathew V *et al.* Efficacy and safety of atrasentan in patients with cardiovascular risk and early atherosclerosis. *Hypertension* 2008; 52: 522–528
18. Black HR, Bakris GL, Weber MA *et al.* Efficacy and safety of darusentan in patients with resistant hypertension: results from a randomized, double-blind, placebo-controlled dose-ranging study. *J Clin Hypertens* 2007; 9: 760–769
19. Weber MA, Black H, Bakris G *et al.* A selective endothelin-receptor antagonist to reduce blood pressure in patients with treatment-resistant hypertension: a randomised, double-blind, placebo-controlled trial. *Lancet* 2009; 374: 1423–1431
20. Bakris GL, Lindholm LH, Black HR *et al.* Divergent results using clinic and ambulatory blood pressures: report of a darusentan-resistant hypertension trial. *Hypertension* 2010; 56: 824–830
21. Rabelink TJ, Kaasjager KA, Boer P *et al.* Effects of endothelin-1 on renal function in humans: implications for physiology and pathophysiology. *Kidney Int* 1994; 46: 376–381
22. Kohan DE. Endothelins in the normal and diseased kidney. *Am J Kidney Dis* 1997; 29: 2–26
23. Goddard J, Johnston NR, Hand MF *et al.* Endothelin-A receptor antagonism reduces blood pressure and increases renal blood flow in hypertensive patients with chronic renal failure: a comparison of selective and combined endothelin receptor blockade. *Circulation* 2004; 109: 1186–1193
24. Dhaun N, Ferro CJ, Davenport AP *et al.* Haemodynamic and renal effects of endothelin receptor antagonism in patients with chronic kidney disease. *Nephrol Dial Transplant* 2007; 22: 3228–3234
25. Orisio S, Benigni A, Bruzzi I *et al.* Renal endothelin gene expression is increased in remnant kidney and correlates with disease progression. *Kidney Int* 1993; 43: 354–358
26. Hocher B, Schwarz A, Reinbacher D *et al.* Effects of endothelin receptor antagonists on the progression of diabetic nephropathy. *Nephron* 2001; 87: 161–169
27. Dhaun N, Macintyre IM, Melville V *et al.* Blood pressure-independent reduction in proteinuria and arterial stiffness after acute endothelin-a receptor antagonism in chronic kidney disease. *Hypertension* 2009; 54: 113–119
28. Wenzel RR, Littke T, Kuranoff S *et al.* Avosentan reduces albumin excretion in diabetics with macroalbuminuria. *J Am Soc Nephrol* 2009; 20: 655–664
29. Sasser JM, Sullivan JC, Hobbs JL *et al.* Endothelin A receptor blockade reduces diabetic renal injury via an anti-inflammatory mechanism. *J Am Soc Nephrol* 2007; 18: 143–154
30. Amann K, Simonaviciene A, Medwedewa T *et al.* Blood pressure-independent additive effects of pharmacologic blockade of the renin-angiotensin and endothelin systems on progression in a low-renin model of renal damage. *J Am Soc Nephrol* 2001; 12: 2572–2584
31. Goddard J, Eckhart C, Johnston NR *et al.* Endothelin A receptor antagonism and angiotensin-converting enzyme inhibition are synergistic via an endothelin B receptor-mediated and nitric oxide-dependent mechanism. *J Am Soc Nephrol* 2004; 15: 2601–2610
32. Dhaun N, MacIntyre IM, Kerr D *et al.* Selective endothelin-A receptor antagonism reduces proteinuria, blood pressure, and arterial stiffness in chronic proteinuric kidney disease. *Hypertension* 2011; 57: 772–779
33. Mann JF, Green D, Jamerson K *et al.* Avosentan for overt diabetic nephropathy. *J Am Soc Nephrol* 2010; 21: 527–535
34. Smolander J, Vogt B, Maillard M *et al.* Dose-dependent acute and sustained renal effects of the endothelin receptor antagonist avosentan in healthy subjects. *Clin Pharmacol Ther* 2009; 85: 628–634
35. Maillard M, Wang Q, Baltatu O *et al.* Do endothelin receptor antagonists induce edema through an extravasation of fluids? Evidence from an experiment in bi-nephrectomized rats. *J Hypertens* 2008; 26 (Suppl 1): 371. Abstract

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